Peri-Operative Brachytherapy In Soft-Tissue Sarcomas. Hospital USM Experience

B Biswal, N Idris, Z Wan, W Ismail, A Halim

Citation

B Biswal, N Idris, Z Wan, W Ismail, A Halim. *Peri-Operative Brachytherapy In Soft-Tissue Sarcomas. Hospital USM Experience*. The Internet Journal of Oncology. 2009 Volume 7 Number 2.

Abstract

Overview: Radiotherapy is an important adjuvant modality in the management of extremity soft-tissue tumors. Interstitial brachytherapy implantation is a precise technique of delivering radiation that conforms to the tumor bed. Materials and Method:Selected extremity soft-tissue sarcomas were managed with wide-excision followed by preoperative implantation of brachytherapy catheters. The implant was irradiated 3-5th day post-surgery to a dose of 3Gy BID for 3-5 days using high dose rate (HDR) system. Further additional external radiotherapy dose of 40- 50Gy in conventional fractionation was delivered to the tumor bed. Observations: 17 patients with soft tissue sarcoma were treated from 2001 to 2007.The median age of patient was 26 years (4-74 years) with male to female ratio of 12:5. Three out of 17 patients develop local recurrence and 7-patient relapse as lung metastases. At the time of reporting, 2-year local control rate was 88% and 24 month overall survival rate was 50%. The complication was minimal and manifested as subcutaneous fibrosis, pigmentation and wound dehiscence. Conclusions: Peri-operative interstitial brachytherapy is an option of radiotherapy for better local control in high grade large volume and recurrent soft-tissue tumor. Proper case selection and optimal multidisciplinary management could improve survival in future.

INTRODUCTION

The primary treatment of soft tissue sarcoma is surgery. In the past, the treatment of choice was amputation, however with the development of surgical technique more conservative surgical excision is considered as the gold standard of management. However local recurrence following surgery is an important shortcoming of primary surgical management. The local relapse rate following amputation range from 20-30% whereas wide-excision result in local recurrence rate of 65% [1]. Postoperative radiotherapy reduces local recurrence following limb salvage surgery. For extremity soft tissue sarcoma addition of adjuvant radiotherapy result in 95% local control rate and <10% amputation rate[2-3]. Currently combination chemotherapy is being employed in most soft tissue sarcoma management protocols[4].

Radiotherapy consisted of classical external beam radiotherapy delivering homogenous radiation dose to the tumor volume (surgical bed) to a dose of 40-50Gy in 4 to 5 weeks in conventional fractionation. With external radiotherapy, the dose conformity is not optimal and often results in complications and growth abnormality among young patients. Interstitial brachytherapy is a conformal form of radiation delivery to the tumor bed that can be delivered peroparative or perioperative period. Brachytherapy is known to improve local control in soft tissue sarcomas with high risk factors [5].

MATERIAL AND METHODS

Patients with extremity sarcomas were evaluated by the muscoskeletal oncology team. The clinical and radiological records of all the patients were reviewed The evaluations consist of biopsy, magnetic resonance imaging (MRI) of primary, computer axial tomography (CT) thorax, whole body bone scintigraphy, Liver and Kidney chemistry, serum LDH level and complete blood count. The tumor volume was evaluated in 3 dimensions from clinical examination and radiological findings. Tissue diagnoses were obtained in all cases with either open or tru-cut biopsy. Patients were evaluated by musculoskeletal oncology surgeon and prior consent was obtained before the brachytherapy procedure. The selection for perioperative brachytherapy include anticipated narrow surgical margin – near to neurovascular bundle, small and closed compartment – foot/ hand or subcutaneous or skin sarcoma with high recurrence rate, high grade sarcomas and recurrent fibromatosis.

SURGICAL TECHNIQUE

Wide resection of the primary tumor with adequate margin

was performed in all cases. Wide resection consisted of removal of the tumour en-bloc with a cuff of normal tissue around the mass according to biological anatomical barrier and magnetic resonance imaging features. The surgical specimens were evaluated for microscopic extent of tumour margin. In large vascular tumors, homeostasis was achieved using selective embolization prior to surgery. After total excision of tumor, the tumor volume was jointly determined by oncologist and surgeons. The surgical radio-opaque clips are placed on 4-margins of the tumor volume.

DETERMINATION OF TUMOR VOLUME

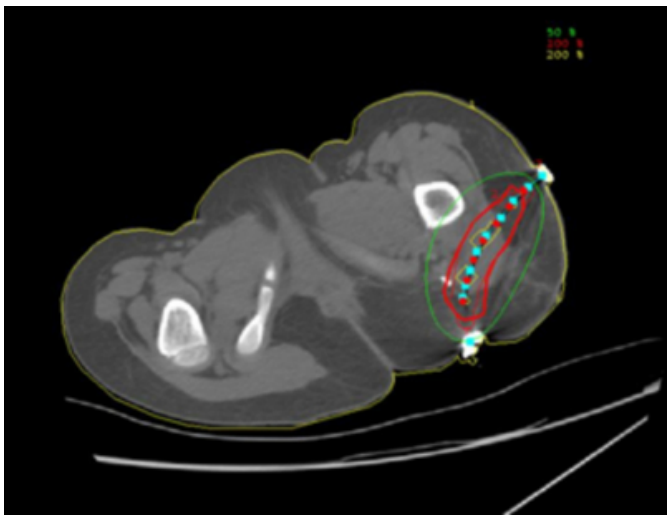
The whole tumor volume with 2cms margin was included in the clinical tumor volume. The removable sterilized interstitial plastic catheters were placed on the surgical bed in longitudinal or horizontal manner at an interval of (separation) 8mm-20mm. The neurovascular bundle were displaced away from the catheter by muscle or fascia and individual catheters were fix to underlying fascia by suturing with absorbable vicryl 3/0 catgut sutures. The drainage tube was kept carefully in the middle of the implant. In large tumors with large tissue defects were filled up by vascular flaps by the reconstruction team. At the end of implant, the catheters were secured by radio-opaque button on the skin surface.

LOCALIZATION

Following surgery, and postoperative recovery on periods the patient were simulated using 2-dimensional orthogonal x-ray images and CT scans. The brachytherapy catheters were identified and dummy wires was placed inside the catheter and orthogonal. localization films were taken from simulator.

Figure 1

Fig-1: CT scan showing position of interstitial brachytherapy catheters showing distribution of isodose around source.

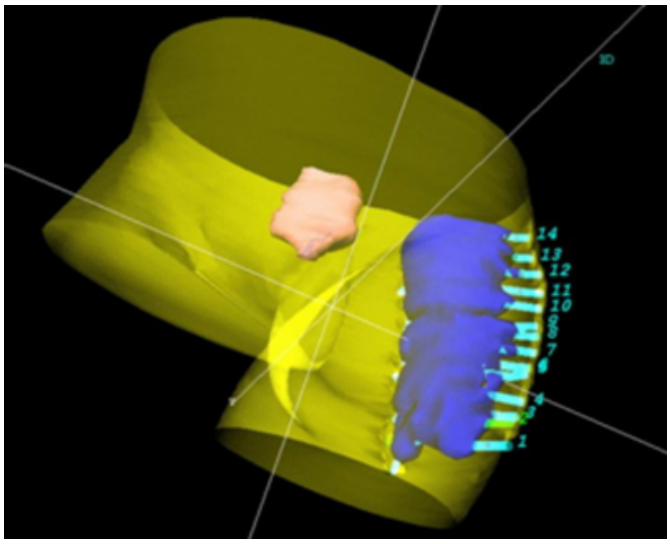


OPTIMIZATION

The catheter position was identified and digitized from radiological images. The images then reconstructed in 3-dimensions. The oncologists draw the tumor volume from the findings of peroperative descriptions and markers. Medical physicist place dwell position of the source to get homogenous radiation distribution. The basal dose, peripheral dose, high dose volume were evaluated. In general we prescribed our radiation dose at 5mm from the mid-center of the source.

Figure 2

Fig-2: 3D constructed image showing isodose cloud around sources in the tumor volume in a case of STS (L) upper thigh



BRACHYTHERAPY PARAMETERS

Brachytherapy plans were evaluated using Nucletron Plato

treatment planning computer. The dose distribution was evaluated at multiple planes. The basal dose rate, high dose volume encompassing 150% isodose diameter around source, cold and hot spot, and dose homogeneity index was evaluated. The reference isodose line was usually 5mm from the center of the source. Dwell position optimization done to obtain homogenous distribution.

BRACHYTHERAPY DOSE AND FRACTION

A dose of 3-4.5Gy was prescribed at above reference point and delivered twice a day at an interval of 6 hours daily for 3-5 days. The radiation was usually delivered 3-5 days post operation using micro-Selectron HDR equipment run on a 10 Ci source. Following irradiation the temporary brachytherapy catheters were removed and dressed with povidone iodine.

SUPPLEMENT EXTERNAL RADIOTHERAPY

Following brachytherapy, the tumor volume was identified and simulated with AP-PA parallel opposed portal. The clinical target volume included gross rumor volume plus 2 cms margin. External radiotherapy was deliver using a 6MV linear accelerator to a dose of 40-50Gy in conventional fractionation to the brachytherapy volume plus 3cms margin.

FOLLOW-UP

The postoperative histopathology was evaluated for surgical margins and poor prognostic factors. Histopathological evaluation mitotic activity of more than 5/high power field and high grade sarcoma, synovial sarcoma, and peripheral neuro-ectodermal tumor (PNET) were advised for chemotherapy. Chemotherapy regimes consisted of doxorubicin (50mg/m2 day-1) and ifosphamide (2000mg/m2 day-1 to day-5 with mesna uroprotection) for 6-cycles in conventional sarcomas. The regimen was repeated every 4 weeks. For PNET sarcomas, we treated with vincristine (2mg day-1), doxorubicin (50mg/m2 day-1) plus cyclophosphamide (500mg/m2 day-1) alternate with ifosphamide (2000mg/m2 day-1 to day-5 with mesna uroprotection) and etoposide (100mg/m2 day-1 to day-5). The regimen was repeated every 3 weeks for 4 cycles. Subsequently patients were followed up at an interval of 3-4 months with clinical and radiological examinations. Serial computed tomography scan of the chest and whole body Technetium 99m MDP bone scan were taken at six monthly intervals for two years and yearly thereafter for five years. Optional local radiological assessments were performed based clinical evidence of recurrence. The outcome of treatment in term of survival and failure were recorded and major complications were documented. The actuarial survival of patients was estimated using Kaplan-Meier's non-parametric method.

OBSERVATIONS

From Jan 2001 to June 2007, we treated 17-cases of soft tissue tumors using perioperative interstitial brachytherapy. There were 12-male and 5 females with median age of 26 years (range 4-47 years). The surgical technique consists of wide excision, re-excision and musculocutaneous flap with reconstruction. The histopathological distribution was hemangiopericytoma (1), malignant peripheral nerve sheath tumor (1), malignant fibrosis histiocytoma (2), leiomyosarcoma (1), fibrosarcoma (1), aggressive fibromatosis (5), synovial sarcoma (2) and primitive neuroectodermal tumor (2), epitheloid sarcoma (1) and dermatofibrosarcoma protruberence (1).

LOCAL CONTROL RATE

Almost all patients achieved good local control except two patients with marginal recurrence treated with 2nd brachytherapy. The first case is a multicentric aggressive fibromatosis and second is a case of recurrent malignant fibrous histiocytoma following post operative radiotherapy.. The overall local control rate was 88%.

DISTANT FAILURE

The major cause of failure was due to a distant metastasis. Seven patients develop pulmonary metastasis and succumb to disease despite of multi agent chemotherapy. Ten (10) patients achieved no evidence of disease status at the time of analysis.

COMPLICATIONS

We encountered 4-cases of subcutaneous fibrosis and pigmentation over brachytherapy site. None of the complication poses cosmetic defect in our series. There was one case of subcutaneous necrosis and wound dehiscence. At the timing of reporting the 24months overall survival rate was 50%.

Figure 3

Fig-3: Kaplan Meier overall survival curve.

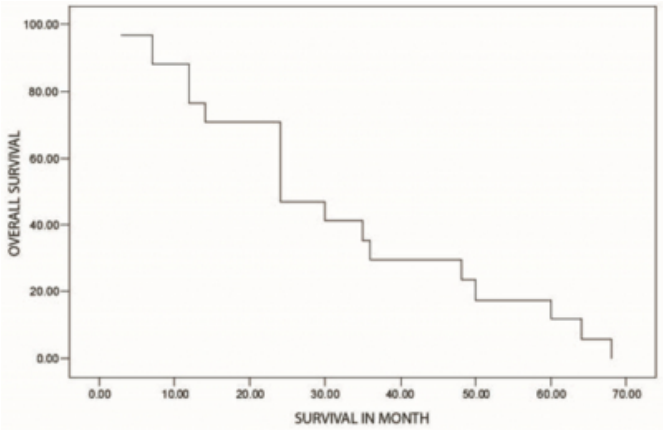


Figure 4

Table-1: Patient and treatment summary

No	Pathology	Site	Resection margin	HDRBr dose	Prescri p tion	No of catheter s	EBRT	Compli cations	Chemo therapy	FU (month)
1	Hemangiopericytome	>20 cms	Positive	3 Gy BD X 3-days	10 mm	10	40Gy	SQ fibrosis	nil	36 NED
2	MPNST	6 cms R forearm	Positive	4.5Gy BID X 2 days	10 mm	4	45 Gy	Nil	Yes	24 DM
3	MFH recurrent	4 cms elbow area	positive	3 Gy BD X 3-days	5 mm	8	Got prior xRT 50Gy+	Skin pigmentati ons	Nil	60 NED
4	Leiomyosarcoma	>10 cms L thigh	Positive	3Gy BD X 3 days	10 mm	9	45 Gy	Nil	Nil	29 NED
5	Fibrosarcoma	>15 cms neck	Positive	3 Gy BD X 3-days	10 mm	9	Got 40 before BRT	Wound dehiscenc e	Yes for lung relapse	24 MD
6	Epithelioid Sarc	4 cms foot	positive	3.5 Gy BID X 3-days	10 mm	8	45 Gy	Nil	Yes for lung mets	24 MD
7	Fibromatosis (rec)	~ 8 cms	positive	3 Gy BD X 3-days	5 mm	12	Nil	Sq fibrosis	Nil	48 PD multicentric
8	Fobromatosis(rec)	plantar	Positive	2.8 Gy BID X 3 days	5 mm	21	Got 60Gy prior xRT	SQ pigmentati on	Nil	32 NED
9	MFH	Left arm	positive	3.5 Gy BID X 3-days	10 mm	10	45 Gy	Nil	Nil	22 NED
10	DFSP	13 cms plantar	Positive	3Gy BD/3-days	5 mm	12	40 Gy	Nil	Nil	18 NED
11	Synovial Sarc	L thigh	Positive	3 Gy BD/3-days	5 mm	8	45 Gy	Nil	Advised but refused	5 NED
12	PNET	~10 cms Gluteal	Positive	2.5 Gy BID X 5-days	5 mm	10	Nil	Nil	On chemoRx	6 NED
13	Fibromatosis (rec)	Left thigh	Positive	3 Gy BD/3-days	5 mm	9	40 Gy	Nil	Nil	60 NED
14	Fibromatosis recurrent	Left thigh	Positive	2.8Gy BID	5 mm	21	Thigh 50Gy+ lower leg 60Gy	Nil	Nil	24 NED
15	Synovial Sarcoma	Right Elbow	Positive	3 Gy BD X 2 days	5 mm	8	25 Gy + 10 Gy after 1 month	Ulcer (Necrosis)	Planning chemo after drying ulcer	3NED
16	Fibromatosis	Left Cubital Fossa	positive	3.5 Gy BID X 2 days	5 mm	6	Nil	Nil	Nil	12 NED
17	PNET	Gluteal region	Positive	2.5 Gy BID X 3 days	5 mm	14	Nil	Nil	Yes for lung mets	12 NED

DISCUSSION

In our experience perioperative interstitial brachytherapy is a feasible option for the management of operable extremely STS. The local control rate in our series was 88% at a median follow-up period of 28-months. The 24-months overall survival was 50% in our series. The main cause of poor survival was due to distant metastasis as seen in 7 of our patients.

Perioperative interstitial brachytherapy is an established radiotherapy technique in the management of localized STS of extremities as a part of limb salvage technique. The functional outcome and quality of life is far superior to amputation or more aggressive surgical procedures. Proper case selection by a multidisciplinary musculoskeletal team improve success rate. Operable localized extremity soft tissue sarcoma, with high grade histology and large tumor volume are suitable for brachytherapy. Perioperative brachytherapy increase local control in high grade tumor. In a study, the local recurrence rate was 22% without brachytherapy verses 3% with brachytherapy[6]. In a randomized clinical trial by Yang et al. involving 141 patients treated with brachytherapy as radiotherapy versus no radiotherapy showed 9% recurrence verses 44% recurrence without radiotherapy (p=0.0003), only 19% received postoperative radiotherapy in this series. However in low-grade sarcomas (n=50), there was 4% local recurrence verses 33% among patients not receiving radiotherapy. However these were no difference in survival[7]. In another trial at MDAH Texas, Pister et al[8]. randomized 164 STS with postoperative brachytherapy versus no brachytherapy. The primary tumor was observed in extremities and upper trunk undergone irradiation after complete wide excision. Sixty eight (68/119) patients with 43 tumors received chemotherapy. The median follow-up was 76 months with 5-year actuarial survival and local control rate of 82% verses 69%. There was no benefit of radiotherapy in lower grade soft tissue sarcoma. However when high grade soft tissue sarcoma was analyses separately, the actuarial local control rate was 89% verses 68% in no brachytherapy group.

Brachytherapy is also necessary for recurrent extremity sarcoma. In our series we treated 3-local recurrences following radiotherapy. Nori et al. studied 40 recurrence soft tissue sarcoma with 45Gy perioperative brachytherapy and achieved 5-year actuarial local control rate of 89% verses 68% with high grade recurrent sarcomas[9]. Another brachytherapy trial from PMH Canada; 10-cases of recurrent extremity STS with re-irradiation. They observed 100% local control rate at a 24 month median follow-up[10].

Another study by Pearlstone[11] from MDAH resulted in local control 65% (17/25 patients) (Pearlstone, versus 82% (33/40) in McGinn's study[12].

Pediatric soft tissue sarcoma poses special challenge to radiation oncologists. Classical external radiotherapy is variably resulting in subcutaneous (SQ) fibrosis and bone growth retardation. In this situation interstitial perioperative brachytherapy is the radiotherapy of choice. It delivers very conformal radiation plus avoids bone growth retardation. Viani et al[13]. studied 18 pediatric STS patients with

perioperative brachytherapy with or without external radiotherapy. The overall local control rate with HBRT alone and HBRT plus XRT were 100% verses 90% respectively. We treated a case of bulky PNET of gluteous muscle with brachytherapy with good local control rate at follow-up of 15-months. In a comparative study a combination of external radiotherapy and brachytherapy results in better local control rate over brachytherapy alone[14].

Though brachytherapy improve long term local control rate, however it does not alter overall survival. The overall survival rate in most series was 70-80% in various series[15]. In our series the actual survival rate is only 50% perhaps due to larger tumor volume and distant metastasis to lung.

Various brachytherapy fractionation schedules have been described in the literature. We used a dose per fraction of 3-4.5 Gy twice a day for 3-5 days where as ABS[16] and NCCN guidelines[17] recommended more protracted fractionation schedule. In patients, especially HDR brachytherapy in pediatric age groups the brachytherapy is use as a sole modality of radiation hence delivered over 6-days period.

Complications of brachytherapy were very minimum in our series. We observed 3 cases of subcutaneous fibrosis with hyper pigmentation. There was another case of subcutaneous necrosis and non-healing ulcer. In earlier series, the complications (acute and late) range from 10-48% depending on series[18-19]. In Viani's series of pediatric patients, they observed 4-cases of wound dehiscence, erythema, telangiestsia and fibrosis[13].

In conclusion perioperative brachytherapy is a unique way to deliver conformal radiation to high risk tumor bed. We achieved better local control rate however, the overall survival rate was only poor due to development pulmonary metastasis most likely due to large volume disease. In future, we should incorporate with modern chemotherapy regimens to improve survival further.

References

1. Alho A, Alvegard TA, Berlin O et al. Surgical margin in soft- tissue sarcoma. The Scandinavian sarcoma group experience. Acta Orthop Scand 1989; 60:687-692
2. Suit HD, Proppe KH, Mankin HJ, Wood WC. Preoperative radiation therapy for sarcoma of soft tissue. Cancer 1981; 47:2869-74.
3. Lindberg RD, Martin RG, Romsdahl MM, Barkley HTJr. Conservative surgery and postoperative radiotherapy in 300 adults with soft-tissue sarcomas. Cancer 1981; 47:2391-2397.
4. Frustaci S, Berretta M, Comandone A et al. Adjuvant treatment of high-risk adjuvant soft-tissue sarcomas: a survey by the Italian sarcoma group. Tumori 2006; 92:92-96.
5. Harrison LB, Franzese F, Gaynor JJ, Brennan MF. Management of extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys 1993; 27:259-65.
6. Brennan MF. Management of extremity sarcoma. Am J Surg 1989; 158:71-8.
7. Yang JC, Chang AE, Baker AR et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol 1998; 16:197-203.
8. Pister PW, Harrison LB, Woodruff JM et al. A prospective randomized trial of adjuvant brachytherapy in the management of low grade soft tissue sarcomas of the extremity and superficial trunk. J Clin Oncol 1994; 12:1150-1155.
9. Noori D, Schupak K, Shiu MH, Bremann MF. Role of brachytherapy in recurrent extremity sarcoma in patients treated with prior surgery and irradiation. Int J Radiat Oncol Biol Phys 1991; 20:1229-1233.
10. Catton C, Davis A, Bell R et al. Soft tissue sarcoma of the extremity. Limb salvage after failure of combined conservative therapy. Radiother Oncol 1996; 41:209-14.
11. Pearlstone D, Janson NA, Fgig BW et al. Re-excision with brachytherapy for locally recurrent soft tissue sarcoma arising in previously irradiated field. Cancer J Sci Am 1999; 5: 20-33.
12. McGinn CJ. Soft tissue sarcoma (excluding retroperitonium) In Principles and Practice of Radiation Oncology. Perez CA, Brady LW, Harlperin EC, Schmidt-Ullrich RK (eds). 4th Eds, Lippincoar Williams, Philadelphia, 2004, 2185-2203.
13. Viani GA, Novaes PE, Jacinto AA et al. High dose rate brachytherapy for soft tissue sarcoma in children: a single institution experience. Radiation Oncology 2008; 3:9.
14. Alekhteyar KM, Leong DM, Brennan MF. The effect of combined external beam radiotherapy and brachytherapy on local control and wound complications in patients with high grade soft tissue sarcoma of the extremity with positive microscopic margin. Int J Radio Oncol Biol Phys 1996; 36: 321-324.
15. Perez CA, Brady LW, Harlperin EC, Schmidt-Ultrich-RK (eds). In Principles and Practice of Radiation Oncology. 4th Eds. Lippincott Williams & Wilkins, Philadelphia, 2004.
16. Nag S, Sasha D, Janjan N et al. The American Brachytherapy Society recommendations for brachytherapy of soft tissue sarcomas. Int J Radiat Oncol Biol Phys 2001; 49:1033-1043.
17. Demetri GD. Pollock R. NCCN Sarcoma practice guidelines. Oncology 1998; 12:183-218.
18. Ormsby M, Hilaris BS, Nori D. Wound complications of adjuvant radiation therapy in patients with soft tissue sarcomas. Ann Surg 1989; 210:93-99.
19. Arbeit J, Hilaris BS, Brennan MF. Wound complications in the multimodality treatment of extremity and superficial truncal sarcomas. J Clin Oncol 1987; 5:480-488.

Author Information

Biswa Mohan Biswal
Department of Nuclear Medicine, Radiotherapy & Oncology, Universiti Sains Malaysia

Nik Ruzman Nik Idris
Department of Nuclear Medicine, Radiotherapy & Oncology, Universiti Sains Malaysia

Zulmi Wan
Musculoskeletal Oncology Unit, Universiti Sains Malaysia

Wan Faisham Wan Ismail
Musculoskeletal Oncology Unit, Universiti Sains Malaysia

Ahmad Shukari Halim
Musculoskeletal Oncology Unit, Universiti Sains Malaysia